II. Information Disclosure Statement

The form PTO-1449 accompanying the prior Official Action issued with respect to the parent application indicated that certain references cited and provided by Applicants could not be located in the Examiner's files. Applicants have previously submitted duplicate copies of these documents, and have requested that they be considered and made of record in the prosecution of the present application. However, such information was not provided in the last Official Action. The Examiner is therefore again requested to initial the previously enclosed Form 1449 to indicate such consideration of these documents. If, however, copies of such resubmitted documents have again been misplaced by the Office, the Examiner is requested to so advise the undersigned by telphone in order that additional copies may be hand carried to the Examiner.

III. The Rejections Pursuant to 35 U.S.C. 112, First Paragraph

Claims 33 and 34 have been rejected under 35 U.S.C. 112, first paragraph in light of their recitation that the N-terminal and C-terminal peptide segments are derived from different families of proteins, which is contented to comprise mew matter. Applicants respectfully traverse and request reconsideration.

Applicants respectfully submit that the specification provides clear evidence that the inventors were in possession of the inventions of claims 33 and 34 at the time the application was filed. In the interest of advancing the prosecution of the present application, Applicants have, however, replaced the term "families" with the term "parent." Clear support for this amendment exists throughout the specification (see, for example, page 5, lines 12-21). Accordingly, Applicants respectfully submit that the rejection of claims 33 and 34 under 35 U.S.C. 112, first paragraph may be properly withdrawn.

Claims 28-36 have been rejected under 35 U.S.C. 112, first paragraph as containing subject matter that is not described in the specification in a manner that would reasonably convey to one of ordinary skill that the inventors were in possession of the invention at the time the application was filed. Specifically, the Examiner has suggested that the specification fails to provide sufficient written description to support a genus of cross-over proteins that are devoid of sequence length, amino acid content, specific biological function as alleged to be produced by the currently claimed method of ligating one or more first proteins with one or more second proteins. Applicants respectfully traverse and request reconsideration.

Applicants have amended the claims to recite that the cross-over proteins are composed of peptide segments that "exhibit sufficient homology to a functional domain of a chemokine, macrophage migration inhibitory factor, cytokine, trefoil peptide, growth factor, protease inhibitor, or protein toxin, to permit said peptide segments to mediate the function of said functional domain when incorporated into said cross-over protein," and respectfully submit that such amendment fully responds to the Examiner's concerns. Applicants submit that those of ordinary skill in the art at the time of the present invention could readily have determined whether a particular peptide segment of a protein imparted a function to the protein, and as such clearly possessed an understanding of how one could determine whether a peptide was or was not a functional domain of a chemokine, macrophage migration inhibitory factor, cytokine, trefoil peptide, growth factor, protease inhibitor or protein toxin. The present claims, as amended, recite that the peptide segments of the claimed cross-over protein possess sufficient homology of sequence and/or structure to such functional domains to impart their function to the cross-over protein. It is respectfully submitted that the amended claims fully comply with the requirements of 35 U.S.C. §112, first paragraph, and that the rejection may be properly withdrawn.

IV. The Rejections Pursuant to 35 U.S.C. 112, Second Paragraph

Claims 28-36 have been rejected pursuant to 35 U.S.C. 112, second paragraph as being indefinite. The Examiner has rejected claim 28 in light of the recitation therein of the word "parent." Applicants have amended the claims to delete this term and respectfully submits that such action fully addresses the Examiner's concerns. Applicants respectfully submit that the rejection may thus now be properly withdrawn.

V. The Rejections Pursuant to 35 U.S.C. 103(a)

A. The Rejections Of Claims 28-31 In Light Of Publications of Canne *et al.* and Dawson *et al.*

The Examiner has rejected claims 28-31 as obvious pursuant to 35 USC § 103(a) in light of Canne *et al.* (J. Amer. Chem. Soc.) and Dawson *et al.* (Science). Applicants respectfully traverse the Examiner's rejection and request reconsideration in light of the amended claims.

The Examiner has concluded that despite this explicit teaching away from the present invention, the cited Canne *et al.* reference nevertheless renders the present invention obvious since it *cites* to a publication (Dawson *et al.*) that concerns native chemical ligation.[1] Applicants again respectfully submit that the Examiner's interpretation fails to address the actual teachings of these references. As discussed previously, Applicants submit that the Canne *et al.* reference teaches the ***C-terminal to C-terminal ligation*** of two peptide domains (see page 2999, first sentence of paragraph bridging left and right columns). Applicants submit that the Dawson *et al.* reference teaches the use of native chemical ligation to synthesize a "non-crossover" protein. At most, the combined teachings of the references would suggest only:

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[1] Although the Official Action refers to some sort of "incorporation" of the Dawson *et al.* publication into the Canne document, the publication is merely cited.

- the use of the process of native chemical ligation (Dawson *et al.*) to produce the molecules exhibiting C-terminal to C-terminal ligation (Canne *et al.*), or

- the coupling of C-terminal to C-terminal residues (Canne *et al.*) to produce a "non-crossover" protein.

Applicants therefore submit that the references cannot be combined to suggest the present invention.

The Examiner's conjecture as to the intent of Canne *et al.* in citing the Dawson *et al.* publication is expressly refuted by the document itself. As Applicants have previously submitted, the citation of the Dawson *et al.* reference in the Canne *et al.* reference is intended to show the use of an alternative – not a conjunctive – chemical synthesis approach. The concept that Canne *et al.* is attempting to communicate is that native chemical ligation (Dawson *et al.*) may be used to create peptides of greater length than those obtainable by conventional synthesis, and that the concepts being disclosed in the Canne *et al.* reference extend this by permitting the synthesis of non-naturally occurring proteins by combining such peptides in non-natural ways. Contrary to the conclusion suggested by the Examiner, the actual teaching that those of ordinary skill would find in the Canne *et al.* reference is as provided at page 2999 of the Canne *et al.* reference:

> "The synthesis of functional protein analogues containing unnatural backbone elements represents an important conceptual breakthrough that demonstrates that we need not be restricted to the formation of native peptide bonds [*i.e., such as the peptide bonds taught by Dawson et al.*] in order to have a biologically active protein."

Accordingly, Applicants respectfully submit the Examiner's rejection of the claims in light of the cited Canne *et al.* reference (alone or in combination with the cited Dawson *et al.* reference) may be properly withdrawn.

B. The Rejections Of Claims 28-36 In Light Of Publications of Canne *et al.*, Dawson *et al.* and Pavia *et al.*

The Examiner has rejected claims 28-36 as obvious pursuant to 35 USC § 103(a) in light of Canne *et al.* (J. Amer. Chem. Soc.) and Dawson *et al.* (Science), and further in light of Pavia *et al.* (Bioorganic Medicinal. Chem. Lett.). The Canne *et al.* (J. Amer. Chem. Soc.) and Dawson *et al.* (Science) references are discussed above. The cited Pavia *et al.* reference is stated to teach the use of combinatorial synthesis strategies in drug discovery. Applicants respectfully traverse the Examiner's rejection and request reconsideration in light of the amended claims.

Applicants respectfully submit that the failure of the cited Canne *et al.* (J. Amer. Chem. Soc.) and Dawson *et al.* (Science) references to render the present invention obvious (see discussion above) is not remedied by the cited Pavia *et al.* reference. Significantly, none of the multiple synthetic approaches discussed in the Pavia *et al.* reference concerns the joining, by any means or in any orientation, of peptide domains of different proteins to form a library of cross-over proteins. Applicants respectfully submit that the cited Pavia *et al.* reference provides no more than a general review of combinatorial chemistry methods unrelated to those of the present invention. As such, the reference, alone or in combination with the cited Canne *et al.* and Dawson *et al.* references, is insufficient to render the present claims obvious.

Accordingly, Applicants respectfully submit the Examiner's rejection of the claims in light of the cited Canne *et al.*, Dawson *et al.*, and Pavia *et al.* references may be properly withdrawn.

VI. The Non-Statutory Double Patenting Rejections

The Examiner has rejected claims 28-36 under the judicially created doctrine of obviousness-type double patenting in light of U.S. Patents No. 6,184,344 and 6,326,468 in view of the above-discussed Canne *et al.* reference, alone or in combination with the cited Pavia *et al.* reference.

In the interest of advancing the prosecution of the present application, and not as an acquiescence to the merits of the Examiner's arguments, Applicants respectfully advise that should the Examiner conclude that the amended claims define patentable and allowable subject matter that would have been obvious in light of the claims of the '344 and '468 patent, Applicants will terminally disclaim such portion of any patent that will issue on such claims that will extend beyond the terms of U.S. Patents No. 6,184,344 and 6,326,468. Applicants agree promptly to provide a Terminal Disclaimer upon notification of such allowable subject matter.

The Examiner has rejected the claims of the application under the judicially created doctrine of obviousness-type double patenting in light of U.S. Patents Nos. 6,184,344 and 6,326,468 in view of the above-discussed Canne *et al.* reference, alone or in combination with the cited Pavia *et al.* reference.

Applicants confirm that, in the interest of advancing the prosecution of the present application, and not as an acquiescence to the merits of the Examiner's arguments, should the Examiner conclude that the amended claims define patentable and allowable subject matter that would have been obvious in light of the claims of the '344 and '468 patent, Applicants will terminally disclaim such portion of any patent that will issue on such claims that will extend beyond the terms of U.S. Patents Nos. 6,184,344 and 6,326,468. Applicants agree promptly to provide a Terminal Disclaimer upon notification of such allowable subject matter.

Having now fully responded to the issues raised by the Examiner, Applicants respectfully submit that the present application is now in condition for Allowance, and earnestly solicit early notice of such favorable action. The Examiner is invited to contact the undersigned with respect to any issues regarding this application.

Respectfully Submitted,

Date: 11/12/2002

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Appendix A: The Nature of the Requested Amendments

To facilitate the Examiner's review of the patentability of the present invention, Applicant has reproduced below the specific nature of the requested amendments.

28. **[Three Times Amended]** A method of producing a cross-over protein that contains at least one peptide segment whose sequence is derived from a first protein, and at least one peptide segment whose sequence is derived from a second protein, wherein said second protein has an amino acid sequence that is different from that of said first protein, and wherein each of said peptide segments possesses an N-terminal amino acid residue and a C-terminal amino acid residue, said method comprising:

ligating under chemoselective chemical ligation conditions (i) at least one peptide segment comprising a functional protein module derived from said first protein, and (ii) at least one peptide segment comprising a functional protein module derived from said second protein, **wherein each of said peptide segments exhibit sufficient homology to a functional domain of a chemokine, macrophage migration inhibitory factor, cytokine, trefoil peptide, growth factor, protease inhibitor, or protein toxin, to permit said peptide segments to mediate the function of said functional domain when incorporated into said cross-over protein,** wherein the C-terminal residue of said peptide segment derived from said first protein and the N-terminal residue of said peptide segment derived from said second protein comprise compatible reactive groups capable of chemoselective chemical ligation to one another, whereby a covalent bond is formed between said compatible reactive groups of said peptide segments so as to produce a chemical ligation product comprising a cross-over protein in which the C-terminal residue of the peptide segment derived from said first protein is ligated to the N-terminal residue of said peptide segment derived from said second

protein**; wherein said first and second proteins are jointly selected from the group consisting of chemokines, macrophage migration inhibitory factors, cytokines, trefoil peptides, growth factors, protease inhibitors, and protein toxins**.

29. **[Twice Amended]** The method of claim 28 further comprising the step of conducting one or more additional ligations with one or more additional peptide segments, each possessing an N-terminal amino acid residue and a C-terminal amino acid residue, **wherein each of said one or more additional peptide segments exhibit sufficient homology to a functional domain of a chemokine, macrophage migration inhibitory factor, cytokine, trefoil peptide, growth factor, protease inhibitor, or protein toxin, to permit said peptide segments to mediate the function of said functional domain when incorporated into said cross-over protein,** wherein said additional peptide segments are selected from the group consisting of a peptide whose C-terminal residue comprises a reactive group capable of chemoselective chemical ligation with a reactive group of an N-terminal residue of another peptide, and a peptide whose N-terminal residue comprises a reactive group capable of chemoselective chemical ligation with a reactive group of an C-terminal residue of another peptide.

30. **[Three Times Amended]** The method of claim 28, wherein the first and second protein molecules from whose sequences said peptides are derived **[**belong to the same family of**]** **are chemokine** protein molecules.

32. **[Three Times Amended]** A method of producing a cross-over protein library whose members contain two or more peptide segments, **wherein each of said peptide segments exhibit sufficient homology to a functional domain of a chemokine, macrophage migration inhibitory factor, cytokine, trefoil peptide, growth factor, protease inhibitor, or protein toxin, to permit said**

peptide segments to mediate the function of said functional domain when incorporated into said cross-over protein, each segment possessing an N-terminal amino acid residue and a C-terminal amino acid residue, and wherein the peptide segments of said members are derived from two or more different proteins, said method comprising:

incubating under chemoselective ligation reaction conditions a plurality of unique peptide segments each comprising one or more functional protein modules derived from a member of a first set of protein molecules and a plurality of unique peptide segments each comprising one or more functional protein modules derived from a member of a second set of protein molecules wherein the C-terminal residues of each of said peptide segments derived from said members of said first set of protein molecules and the N-terminal residue of each of said peptide segments derived from said members of said second set of protein molecules comprise compatible reactive groups capable of chemoselective chemical ligation to one another, whereby a covalent bond is formed between said compatible reactive groups of said peptide segments so as to produce a plurality of chemical ligation products comprising a plurality of unique cross-over proteins, wherein, for each such cross-over protein, the C-terminal residue of a peptide segment derived from a member of said first set of protein molecules is ligated to the N-terminal residue of a peptide segment derived from a member of said second set of protein molecules**; wherein said first and second proteins are jointly selected from the group consisting of chemokines, macrophage migration inhibitory factors, cytokines, trefoil peptides, growth factors, protease inhibitors, and protein toxins**.

33. [**Three Times Amended**] The method of claim 32, wherein said [plurality of peptide segments derived from members of said first set of protein molecules are obtained by cross-over ligation of two or more different families of] **first and**

second set of proteins from whose sequences said peptides are derived are chemokine protein molecules.

34. [**Three Times Amended**] The method of claim 32, wherein said **[**plurality of peptide segments derived from members of said second set of protein molecules are obtained by cross-over ligation of two or more different families of**]** **first and second set of proteins from whose sequences said peptides are derived are cytokine** protein molecules.

35. [**Four Times Amended**] The method of **[**claim 32**]** **claim 28**, wherein **[**said**]** **the** first and second protein molecules **from whose sequences said peptides are derived** **[**belong to the same family of**]** **are cytokine** protein molecules.